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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/058,292	01/30/2002	James L. Hartley	0942.285000H/RWE/BJD	3058

26111 7590 08/09/2006

STERNE, KESSLER, GOLDSTEIN & FOX PLLC
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
GUIDRY, GUY L	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 08/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/058,292	HARTLEY ET AL.	
	Examiner	Art Unit	
	Guy Guidry, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *187-219,223-225 and 228-248* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *187-219,223-225 and 228-248* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 December 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date ~~5/18/2006~~ 6-5-06.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of a response filed 18 May 2006 to the Office Action mailed 18 November 2005. Claims 1-186, 220-222, 226-227 are canceled in this application. Claims 187-219, 223-225, 228-248 are currently pending and under consideration in this Action. As Applicant's arguments apply equally to each of the three statements of rejection under 35 USC § 103 herein below, a single response to Applicant's arguments is forth following all of the statements of rejection repeated herein.

Information Disclosure Statement

With respect to the IDS filed 5 June 2006, it is desirable to avoid the submission of long lists of documents if it can be avoided. Eliminate clearly irrelevant and marginally pertinent cumulative information. If a long list is submitted, highlight those documents which have been specifically brought to applicant's attention and/or are known to be of most significance. MPEP § 2004. 13.; *See Penn Yan Boats, Inc. v. Sea Lark Boats, Inc.*, 359 F. Supp. 948, 175 USPQ 260 (S.D. Fla. 1972), aff 'd, 479 F.2d 1338, 178 USPQ 577 (5th Cir. 1973), cert. denied, 414 U.S. 874 (1974). *But cf. Molins PLC v. Textron Inc.*, 48 F.3d 1172, 33 USPQ2d 1823 (Fed. Cir. 1995).

The Office Actions and the unpublished applications cited in the Disclosure Statement have been initialed considered by the Examiner, however Office Actions are not suitable for publication as Reference Cited when/if claims are deemed allowable and a patented granted. Therefore, the references have also been lined through.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 187, 190-193, 196-199, 201-206, 210-211, 213, 216-217, 223-225, 228, 231-232, 235-237 and 247-248 stand rejected under 35 U.S.C. 103(a) as being unpatentable Fukushige et al. (PNAS. 1992; 89:7905-09; of record), further in view of Abremski et al. (J. Biol. Chem. 1984; 259:1509-14), Griffiths et al. (US 5,962,255), Senecoff et al. J. Mol. Biol. 1988; 201; 405-21) and Johnson et al. (WO/93/191172; of record).

This is rejection is of record. Salient features of the rejection are repeated herein below in abbreviated form. The claims are directed to a method of producing a nucleic acid molecule through recombination of two nucleic acid molecules each comprising a recombination site, which provide substrates for site-specific recombinase thus combining portions of an antibiotic resistance gene to form a functional gene. The secondary references on whole provide support for conducting *in vitro* reactions utilizing site-specific recombination sites and recombinase proteins, as well as demonstrating the particular functional equivalency of various site-specific recombination sites/recombinases in conducting *in vitro* (or *in vivo*) recombination between two nucleic acid molecules to form functional genes.

Fukushige et al. teach nucleic acid molecules involved in site-specific recombination. Fukushige does not specifically state that nucleic acid molecules or the recombinase protein are present *in vitro*.

Indeed, to conduct *in vitro* recombination reactions so as to produce the resulting nucleic acid molecules (e.g., vectors) would entail nothing more than routine experimentation, given the level of skill at the time of invention. For example, Abremski et al. teaches that *cre* recombinase and nucleic acid molecules comprising *lox*P sites are isolated and present *in vitro* where a site-specific recombination reaction occurs. (e.g., Abstract; p. 1509, col. 2, ¶ 1; p. 1510, col. 1, ¶ 1; p. 1512, last ¶, bridging to p. 1513, col. 1). Furthermore, for *in vitro* recombination, Abremski et al. teaches that cofactors or accessory proteins are not required for efficient recombination. (e.g., p. 1513, col. 1, ¶ 1). It is noted that with respect to intermolecular recombination both Cre

recombinase and Int, Xis and IHF as well as γδ resolvase all appear to act stoichiometrically during recombination. (e.g., p. 1513, col. 2, ¶ 4). In other words, increased efficiency of recombination reactions concentrations for a given combination of components results from increasing concentrations.

However, the salient point is that Abremski et al. set out the *in vitro* conditions necessary to effectuate site-specific recombination for a *Cre/lox* system. (e.g., p. 1510, col. 1, under *Assay for Recombination in vitro*). Moreover, the reference teaches that *Cre* can carry intermolecular or intramolecular recombination between two *loxP* sites. (e.g., p. 1513, col. 1, first full ¶).

In addition, regarding *in vitro* recombination utilizing site-specific recombination sites, Johnson et al teach methods for producing members of specific binding pairs featuring the use of recombinant bacteriophage to display functional antibodies (e.g. scFv; see, for example, pages 19, 26-34, 46-47, 49 and 52).

Therefore it would have been obvious to isolate any nucleic acid molecule, including those that Fukushige teaches so that nucleic acid molecule comprising *lox*P sites and the *cre* recombinase protein are present *in vitro*. One of skill would be motivated to isolate said compositions so as to obtain the benefit and convenience of assaying particular site-specific recombination reactions *in vitro*. Moreover, given the level of skill at the time of invention and the remedial nature of the steps required to isolate nucleic acid molecules and active recombinase proteins such as *cre*, there would have been a reasonable expectation of success in isolating the nucleic acid molecules

and *cre* protein that Fukushige teaches, so as to conduct recombination reactions *in vitro*.

As far as site-specific recombination systems (i.e., recombinase proteins and binding sites) are concerned lambda phage *att* sites were routinely utilized in the relevant art interchangeably with other site-specific recombination systems (e.g.,Cre/*lox*, FLP/*Frt*, Int/*att*). Indeed, as Griffiths et al. state, "One of the most fully understood site-specific recombination systems is that used in integration and excision of bacteriophage lambda". (col. 19, l. 17). Moreover, Griffiths et al. essentially discuss both the *lox* and *att* systems in the context of site-specific recombination as interchangeable. (e.g., col. 19; especially ll. 19-48; claims 194, 195, 200, 228, 235-238). In addition, as noted above, Johnson et al. teach that recombination sites can be *loxP* or *att* sites and that recombinases can be Cre, Int, IHF, Xis, Flp, Tn3, Gin or Cin. (Supra, Johnson et al, pp. 26-34 ; claims 194, 195, 200, 228, 235-238).

As such, it would have been obvious to modify the nucleic acid molecules taught by Fukushige to utilize additional recombination sites/recombinases. One would have been motivated to make such a modification to obtain the benefit of extending the range of site-specific recombination systems (recombinases and their cognate substrate/recognition sites). Furthermore, given the level of skill at the time of invention, there would have been a reasonable expectation of success to substitute one site-specific recombination system, as taught by Fukushige, with the Int/*att* system as discussed by Griffiths et al. or Johnson et al.)

Claims 187-219, 223-225, 228-238 and 247-248 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Fukushige, Abremski, Griffiths, Senecoff and Johnson, further in view of Lenski et al. (J. Bact. 1994; 176: 3140-47; reference of record).

This rejection is of record and repeated in abbreviated for herein below consonant with interpretations above; the teachings of all the cited references are incorporated and applied herein to the rejected claims. Additional embodiments are directed to chloramphenicol as the antibiotic resistance gene and the host cell as bacterial, in particular *Escherichia coli.*

Fukushige does not explicitly teach chloramphenicol as the antibiotic gene, nor that *E. coli* bacterial cells are host cells in methods involving recombinases and site-specific recombination substrates on different nucleic acid molecules.

As discussed above, Johnson et al. and Griffith et al. both teach methods of recombination between nucleic acid molecules comprising recombination sites as substrates for a given recombinase, which recombination reaction results in functional genes, including antibiotic genes, that are utilized to select nucleic acid molecules/cells comprising the functional gene.

Indeed, Johnson et al teach that *E. coli* is easily adaptable to recombinases, including those acting on *lox* and *att* recombination sites. Furthermore, *E. coli* has been a staple bacterial/prokaryotic host organism utilized for a various molecular biological techniques and selection of *E. coli* as well as other bacterial cells is routinely based on selection markers, including antibiotic resistance genes. For example, Lenski et al.

teach several different antibiotic resistance genes that can be used as selection markers and to enhance bacterial fitness in one of the most widely studied and utilized bacterial species – *E. coli*.

Therefore, it would have been obvious to use a host of different antibiotic genes, such as chloramphenicol, in the expression vectors that are taught by Fukushige so as to extend the range of antibiotic resistance genes (i.e., selection markers), and where said selection markers correspond to a particular host organism/cell. Thus, it would have been obvious to use a recipient cell, such as *E. coli*, in which a particular antibiotic resistance gene, such as chloramphenicol will relate to a phenotypic selection as Lenski teaches.

One would have been motivated to use different antibiotic genes and different host cells to obtain the benefit of an extended range of antibiotics and to use widely available and easily propagated cells. In fact, whether the nucleic acid molecules undergo a reaction *in vitro*, in a CHO cell or in an *E. coli* cell, the combined teachings of the cited art teaches that such a reaction would be routine and involve nothing more than remedial steps, as suggested by Fukushige, Senecoff, Abremski, Griffith and Johnson et al.

Claims 187-219, 223-225 and 228-248 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Fukushige, Abremski, Griffiths, Senecoff and Johnson, Lenski et al. (J. Bact. 1994; 176: 3140-47; reference of record) further in view of Wahl et al. (US 5,677,177).

This rejection is of record and repeated in abbreviated for herein below consonant with interpretations above; the teachings of all the cited references are incorporated and applied herein to the rejected claims. Additional embodiments are directed to either the first or second nucleic acid molecule comprising an additional recombination site. (claims 239-246).

Fukushige, Abremski, Griffiths, Senecoff do not specifically teach that one of the two nucleic acid molecules can comprise an additional recombination site.

However, Johnson et al specifically teach that the nucleic acid molecules can comprise an additional recombination site. (e.g., pp. 22-23). In addition, Wahl et al teach that as between two nucleic acid molecules one can comprise an additional recombination site, whereby a recombinase-mediated recombination event leads to excision of the target site-bounded fragment comprising the single recombination site. (e.g., col. 6, ll. 25-36; Fig. 1B).

Therefore, it would have been obvious, in light of the teachings of Johnson and Wahl to include an additional recombination site on one of the target nucleic acid molecules as taught by Fukushige. One would have been motivated to make such a modification to obtain the benefit of extending the range/number of potential recombination events between to nucleic acid molecules, such as excision of a target portion of a gene, as taught by Wahl. Furthermore, given the level of skill in the art at the time of invention, it would have entailed nothing more than remedial steps to incorporate an additional recombination site into a nucleic acid molecule.

Response to arguments

Applicant argues that the Fukushige reference serves as the primary reference in each of the three 103 rejections and that Fukushige discloses only *in vivo* recombination reactions, not *in vitro* recombination reactions as required by the instant claims. Applicant argues the Fukushige recombination reactions involve chromosomal DNA and that chromosomal DNA involved in the Fukushige recombination reactions is not an isolated nucleic acid molecule as required by the instant claims. Applicant argues that Fukushige's *in vivo* recombination reactions are 180 degrees different from the recombination reactions of the instant inventions. Applicant further argues that the skilled artisan reading Fukushige would be lead to follow a completely different path (inside of cells) than that presently claimed (outside of cells) and thus Fukushige clearly teaches away from the presently claimed invention. Thus, the crux of Applicant's argument is that because Fukushige fails to teach *in vitro* recombination, Fukushige teaches away from the instant inventions rendering and therefore Fukushige cannot serve as the basis for a proper 103 rejection and none of the secondary references correct this alleged defect.

Applicant's arguments have been considered in full and they are not persuasive. First, the Office notes that Fukushige is drawn to recombination in isolated cells in culture (p. 7905,col. 2 ¶4 to p. 7906), not in a living organism. Therefore, Fukushige teaches *in vitro* recombination and isolated nucleic acids, as would be understood by a person of ordinary skill in the art and makes obvious, in combination with the secondary references, the instant claimed invention (see Compact Oxford English Dictionary and

The American Heritage® Dictionary of the English Language defining *in vitro* to mean in a test tube, culture dish or elsewhere outside a living organism).

Further, as the Office previously pointed out in detailing the foregoing rejections, the secondary references on whole provide support for conducting *in vitro* reactions utilizing site-specific recombination sites and recombinase proteins, as well as demonstrating the particular functional equivalency of various site-specific recombination sites/recombinases in conducting *in vitro* (or *in vivo*) recombination between two nucleic acid molecules to form functional genes. The rejections make clear that the secondary references show that the rejected claims encompass subject matter that is unmistakably *prima facie* obvious in view of said references.

In determining the differences between the prior art and the claims, the question under 35U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983). A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). However, "the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed...." In re Fulton, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004).

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). All three criteria were fully met in the foregoing rejections, as is clear in extensive analysis and discussion (referring to the 11/18/2005 Office Action), that motivation to combine teachings of the cited references with a reasonable expectation of success (p. 7, ¶2, p. 10, ¶¶2-3, p. 11, ¶4) are manifestly evident and all of the limitations of the instant claims are met by the combined references (see the entire 11/18/2005 Office Action).

Further, the advantages gained by modifying the *in vivo* recombination reaction of Fukushige for use *in vitro* (for example basic studies of gene targeting, promoter activation, vector construction, etc.) would have been *prima facie* obvious to a person of ordinary skill in the art at the time of the instant invention.

The Office finds no evidence to support Applicant's argument that Fukushige cannot serve as the basis for a proper rejection under 35 USC § 103 and that none of the secondary references correct the alleged defect. On the contrary, a *prima facie* case of obviousness has been established, including motivation to combine teachings of the

exemplary secondary references, which, in combination with Fukushige, make obvious instant claimed inventions

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Guy Guidry, Ph.D. whose telephone number is 571-272-7928. The examiner can normally be reached on Monday through Friday 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Guy Guidry, Ph.D.

Examiner

Art Unit 1636

DANIEL M. SULLIVAN
PATENT EXAMINER